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Evaluation of the Pharmacological Activity of New Synthesized 2-phenyl Benzimidazoles Derivatives

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ABSTRACT

A novel series of 2-phenyl benzimidazole derivatives were synthesised by cyclocondensation with appropriate reagents. The structures of all the synthesized compound were characterized by UV, FTIR, ^{1}H NMR, mass spectroscopy and elemental analysis. All the compounds were also evaluated for antibacterial activity against gram-positive bacterial strains like Bacillus subtilis and Streptococcus aureus, and gram-negative bacterial strains like Escherichia coli and Pseudomonas aeruginosa. Some of the compounds inhibited the growth of gram- positive bacteria (*B. subtilis* and *S. aureus*) at MIC values between 10 and 100 mg/mL. Some of the compounds exhibit antimicrobial activity against gram negative bacteria (*E. coli* and *P. Aeruginosa*) MIC values between 10 and 100 mg/mL.

Keywords: Benzimidazoles, Antimicrobial activity, Cyclocondensation.

INTRODUCTION

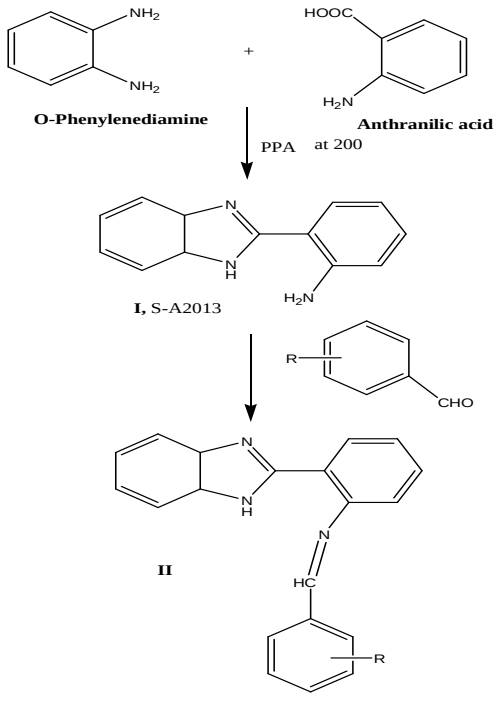
Benzimidazole derivatives have occupied a prominent place in medicinal chemistry because of their significant properties as therapeutics in clinical applications. Benzimidazole derivatives are an important class of nitrogen containing heterocycles and which is the most promising heteroaryl moiety has yielded many successful drugs[1]. Benzimidazole, in an extension of the well elaborated imidazole system, has been used as carbon skeletons for N-heterocyclic carbenes. The

NHCs are usually used as ligands for transition metal complexes. Various biological activities reported on benzimidazole derivatives are antioxidant[2,3] anti-inflammatory[4,5], analgesic[6], anti-hepatitis-B-virus[7] antihypertensive[8], anthelmenthic[9,10,11], anti-protozoal[12,13], anticance[14] and antimicrobial[15-20].

There are two general methods for the synthesis of 2-substituted benzimidazoles. One is the coupling of phenylenediamines and carboxylic acids[21] or their derivatives (nitriles, imidates,or ortho esters)[22], which often requires strong acidic conditions and sometimes combines with very high temperatures (i.e., PPA, 180◦C) or the use of microwave irradiation[23]. The other way involves a two-step procedure that includes the oxidative cyclo-dehydrogenation of aniline Schiff's bases, which are often generated in situ from the condensation of phenylenediamines and aldehydes. An number of heterocyclic compounds of medicinal interest have already been reported[24,25]. Benzimidazole containing drugs have broadened scope in remedying various dispositions in clinical medicine[26]. Owing to the importance and in continuation of our ongoing project work on benzimidazole derivatives, it was felt worthwhile to synthesize some novel 2-phenyl benzimidazoles derivatives and screen them for antibacterial activity.

EXPERIMENTAL

Melting points were determined with an electrothermal melting point apparatus and were uncorrected. Commercially available reagent grade chemicals were used as received. All reactions were followed by TLC, with detection by UV light and/or spraying a 20% KMnO 4 aq. Solution column chromatography was carried out on silica gel (60-120 mesh, E. Merck). IR spectra were recorded as thin films or in chloroform solution with a Shimadzu (4000-450 cm -1) FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker Biospin Avance-III 800 MH_z NMR (Bruker GmBH, Germany) Topspin software. Chemical shift values are reported in ppm relative to SiMe 4 as internal reference, unless otherwise stated; s (singlet), d (doublet), t (triplet), m (multiplet); J in hertz. FAB mass spectra were performed using a mass Spectrometer Jeol SX-102 and ESI mass spectra with API-4000 (Applied Biosystems).



Scheme-I

General procedure for the preparation of the 2-(2-aminophenyl) benzmidazole (S- A, I) and Schiff bases (II)

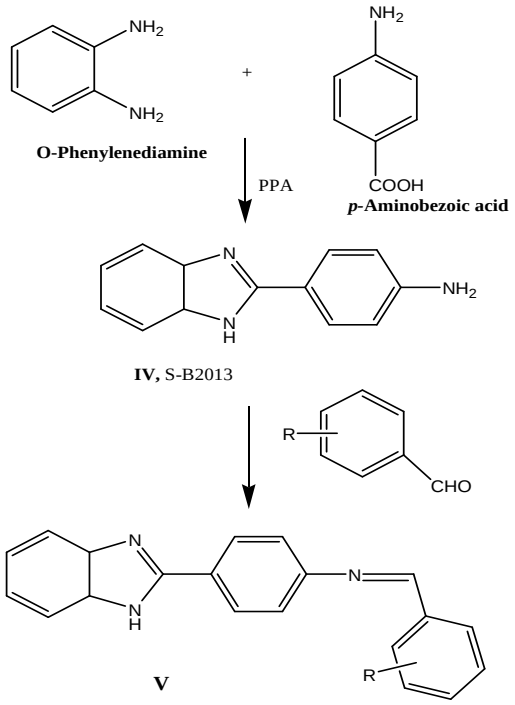
o-Phenylenediamine was condensed with anthranilic acid in poly phosphoric acid at 200◦C for 5 h. The reaction mixture was poured into ice. Filtered, washed, dried and recrystalized. The product 2-(2-aminophenyl) benzimidazole (S-A, I) was then treated with various aromatic aldehydes to obtain the Schiff bases compounds (II).

Table 1. Schiff bases derived from 2-(2- amino phenyl) benzimidazole (S-A2013).

Serial no.	Compound code	Substitution R	Molecular Formula	Molicular weight	Melting point	% yield	Rf Value
1	S-117	H	$C_{20}H_{15}N_3$	297.13	199-205	45	0.79
2	S-111	2-OH	$C_{20}H_{15}N_3O$	313.35	260-265	65	0.66
3	S-116	3-NO_2	$C_{20}H_{14}N_4O_2$	342.35	215-218	78	0.73
4	S-115	3-OCH_3	$C_{21}H_{21}N_3O_2$	343.13	266-268	59	0.68
5	S-115-1	4-OCH_3	$C_{21}H_{17}N_3O$	327.13	241-243	51	0.53

Table 2. Schiff bases derived from 2-(4- aminophenyl) benzimidazole (S-B2013).

Serial no.	Compound code	Substitution R	Molecular Formula	Molicular weight	Melting point	% yield	Rf Value
1	S-210	H	$C_{20}H_{15}N_3$	297.13	211-212	44	0.75
2	S-208	2-OH	$C_{20}H_{15}N_3O$	313.35	244-245	75	0.63
3	S-202	3-NO_2	$C_{20}H_{14}N_4O_2$	342.35	255-256	80	0.66
4	S-209	3-OCH_3 4-OH	$C_{21}H_{21}N_3O_2$	343.13	231-2232	60	0.62
5	S-204	4-OCH_3	$C_{21}H_{17}N_3O$	327.13	221-223	58	0.59



Scheme-II

Preparation of 2-(4- aminophenyl) benzmidazole (S-B, IV) and Schiff bases (V)

In another sequence of reactions, o-phenylenediamine was condensed with *p*-amino benzoic acid in poly phosphoric acid at 200◦C for 5 hours. The reaction mixture was poured into ice. The product was than filtered, washed, dried, and recrystalized. The product 2-(4-aminophenyl) benzimidazole (S-B, IV) was then treated with various aromatic aldehydes to obtain the Schiff bases compounds (V).

RESULTS AND DISCUSSION

The antibacterial activity of all of the compounds against *S. aureus* and *B. subtilis* as gram positive and *E. coli* and *P. aeruginosa* as gram negative bacteria showed lower potencies than the control drug ampicillin. Some of the compounds (S-111, S-202, S-115, S-116 and S- 208)

showed good activity with a MIC value of 23 µg/mL against *P. aeruginosa*, which was comparable to ampicillin.Compound S-202 and S-210 exhibited significant activity against *B. subtilis* with a 25 g/mL. As a result of antimicrobial activity, substitution of amine function to anilide at the 2-phenyl moiety of benzimidazole ring increases the activity against *B. subtilis*.

CONCLUSION

In conclusion, we have described a simple protocol for the synthesis of 2-(2-amino phenyl) benzimidazole and 2-(4-amino phenyl) benzimidazole with remarkable yields. This method was able to give reasonably good and clean yields. Ten derivatives were prepared and biologically evaluated for antibacterial activity. All the synthesized compounds were screened for their in-vitro antibacterial activities. The pharmacological activities exhibited by synthesized novel benzimidazole derivatives have confirmed that these compounds may serve the purpose of being accepted as the novel therapeutic agents. Furthermore, an extensive toxicological study of these derivatives are highly recommended to assess the safety and pharmacological efficacy of the compounds studied.

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